REMARKS

By the present communication, no claims are amended, canceled, or added. Thus, claims 1-15 are pending in the Application. In view of the reasons that follow, Applicants respectfully request reconsideration of the present application.

I. Examiner Interview Summary

Applicant's Representative, the undersigned, thanks Examiner Davis for courtesies extended in the telephonic interview on February 20, 2009. During the interview, the finality of the rejection as well as the enablement of claims 1-15 was discussed. The Examiner indicated that the finality of the rejection was premature and would be withdrawn. The Examiner expressed concern that the application does not show which modification of torasemide the claimed process produces and that Applicants might be relying on incorporation by reference of essential subject matter. The Examiner further expressed concern as to whether the claimed method was different than that set forth in *Acta Cryst.* B34 (1978), 1304-1310. Applicant's representative attempted to allay the Examiner's concerns and agreed to present the following remarks in a timely filed response.

II. Finality of the Rejection

As a preliminary matter, Applicants respectfully request withdrawal of the finality of the Office Action. Claims 1-15 were previously rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Topfmeier *et al.*, U.S. Patent No. 4,743,693; Dreckmann-Behrendt *et al.*, U.S. Patent No. 6,166,045; and Rollinger *et al.*, *Eur. J. Pharm. Biopharm.* 53:75–86 (2002). The Examiner withdrew this rejection based on the response filed Sept 3, 2008 (see p. 2, Office Action). A new rejection under 35 U.S.C. § 112 is cited in the current Office Action and is not previously of record. Further, Applicants did not make any amendments to the claims in their last response. Because the new rejections were not necessitated by amendments, Applicants are entitled to an opportunity to respond to the new rejection. Applicants therefore request that the

finality of the rejection be withdrawn pursuant to the procedure provided at MPEP § 706.07(a) and as indicated during the Examiner interview.

III. Rejections Under 112, First Paragraph

The Office Action rejects each of claims 1-15 under the first paragraph of 35 U.S.C. § 112 alleging that they fail to comply with the enablement requirement. Specifically, the Office Action states, "The specification is silent and fails to provide guidance as to whether the sample of modification I of torasemide is obtained", and that "there are no working examples which disclose the IR spectrum and X-ray powder pattern of the sample of modification I of torasemide obtained by the claimed process." The Examiner finally concludes that "a person skilled in the art would have to engage in undue experimentation to determine which modification I of torasemide corresponds to the instantly claimed process, with no assurance of success". Applicants respectfully traverse this rejection for the reasons discussed below.

The present invention relates to a novel process for the preparation of a known polymorphic form, namely, modification I of torasemide. Applicants submit that the specification sufficiently enables one skilled in the art to prepare and characterize the crystalline modification I of torasemide using the currently claimed process. Examples 1 and 2 of the specification provide sufficient guidance for one skilled in the art to synthesize the modification I and confirm its structure by a comparison of the IR spectrum and the X-ray powder pattern of the modification obtained by the currently claimed process with that of an authentic sample of modification I of torasemide obtained according to reference *Acta Cryst.* B34 (1978), 1304-1310 (hereinafter, "the Dupont article.")

Applicants submit that referencing the Dupont article to establish that the product of the claimed process matches a known product does not rely on incorporation of essential subject data by reference. Torasemide modification I is a well known polymorph of torasemide characterized in the Dupont article as having a melting point of 169 °C and monoclinically crystallizing in the space group $P2_1/c$. Modification I has routinely been the subject of patent and journal publications which refer back to the Dupont article. Representative examples include:

(a) *Eur. J. Pharm. Biopharm.*, 53, (2002), 75-86, (cited in Applicants' Information Disclosure Statement and in the Office Action of June 3, 2008) discloses characterization of three modifications of torasemide, namely, modification I, modification II and form A. The publication provides an FTIR spectrum (Fig. 5, p 80) and an X-ray powder pattern (Fig 7, p 81) of modification I in additional to other characterization data such as DSC and TGA. After presenting this comparative data, the authors, in col 2, p 85 of the publication, conclude that "the two crystal structures published in 1978 [4,5] are representing mod. I (monoclinic, $P2_1/c$, Dupont's form I) and form A (monoclinic, P2/n, Dupont's form II)." Reference no. 4 is the Dupont article referred to in Applicants' specification. Thus, it is evident that the polymorph in the Dupont article is modification I of torasemide, and that the XRPD and IR data of this polymorph are readily available to the skilled artisan for comparison.

(b) Topfmeier *et al.*, U.S. Patent No. 4,743,693 references the Dupont article and a second article by the same authors to establish that torasemide is known to exist in two modifications (I and II) which differ X-ray crystallographically. The differences are briefly described (see col. 1, lines 24-40). Further, in Examples 1 and 2, which are directed to the production of modification I of torasemide, Topfmeier, by way of characterization, notes that the X-ray diffraction diagram of the product corresponds to that of the pure modification I. No characterization data were provided. The clear implication is that the inventors compared analytical data for their product with data known in the art, i.e., data in the Dupont article, and that modification I is so well known that it is not necessary to provide characterization data available in the art.

(c) Dreckmann-Behrendt *et al.*, U.S. Patent No. 6,166,045, contains virtually the same disclosure as Topfmeier regarding the Dupont article (see col. 1, lines 26-43).

Based on the above references, it is evident that modification I of torasemide is well known in the art, and that one skilled in the art would be able to readily verify that Applicant's claimed process produces modification I of torasemide. Thus, the skilled artisan would not have

to engage in undue experimentation to determine which modification of torasemide is produced by the claimed process. Applicants therefore request withdrawal of the present rejection.

In one further note, Applicants acknowledge the Examiner's concern during the interview as to what the Dupont article discloses with respect to the method of making modification I of torasemide. Under the experimental part on p. 1305 of the Dupont article, it is disclosed that the torasemide used for the crystallization experiments was provided by a third party. The torasemide was then crystallized from petroleum ether and ethanol. This process was described by Topfmeier (col. 1, lines 24-40) and Dreckmann-Behrendt *et al.* (col. 1, lines 26-43) and on page 2 of the present application:

> it is known that modification I of torsemide and modification II of torasmide crystallize simultaneously when a torasemide solution in a solvent mixture petroleum ether/ethanol slowly evaporates [*Acta Cryst.* B34 (1978), 1304-1310]. Such a manner of preparation, however, wherein both modifications crystallize from the same solvent mixture and hence must be separated with regard to their macroscopic crystal form, is certainly not suitable for large-scale production.

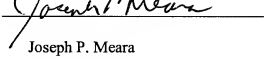
Thus, the Dupont article does not disclose how torasemide was prepared, but only how modifications I and II of torasemide were obtained. As set forth in Applicants' previous response, the claimed method produces modification I of torasemide directly from the alkaline extract of the original reaction mixture of a last phase in the synthesis of torasemide. It does not depend on a separate crystallization step as described in the Dupont article. As such, Applicants respectfully submit that the claimed methods are patentable over the Dupont article.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. If any issues remain to be resolved in view of the present response, the Examiner is invited to contact the undersigned by telephone to expedite the prosecution of the present application.

Respectfully submitted,

Dated: February 26, 2009

By 

FOLEY & LARDNER LLP
Customer Number: 23524
Telephone: (608) 258-4303
Facsimile: (608) 258-4258

Joseph P. Meara
Attorney for Applicant
Registration No. 44,932